VOLUME 29 · NUMBER 35 · DECEMBER 10 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Study of Intraperitoneal Paclitaxel Plus Cisplatin and Intravenous Paclitaxel Plus Bevacizumab As Adjuvant Treatment of Optimal Stage II/III Epithelial Ovarian Cancer

Jason A. Konner, Diana M. Grabon, Scott R. Gerst, Alexia Iasonos, Howard Thaler, Sandra D. Pezzulli, Paul J. Sabbatini, Katherine M. Bell-McGuinn, William P. Tew, Martee L. Hensley, David R. Spriggs, and Carol A. Aghajanian

Jason A. Konner, Diana M. Grabon, Scott R. Gerst, Alexia Iasonos, Howard Thaler, Sandra D. Pezzulli, Paul J. Sabbatini, Katherine M. Bell-McGuinn, William P. Tew, Martee L. Hensley, David R. Spriggs, and Carol A. Aghajanian, Memorial Sloan-Kettering Cancer Center, New York, NY.

Submitted March 25, 2011; accepted September 2, 2011; published online ahead of print at www.jco.org on November 7, 2011.

Supported in part by Genentech.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Jason A. Konner, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10065; e-mail: konnerj@mskcc.org.

0732-183X/11/2935-4662/$20.00

DOI: 10.1200/JCO.2011.36.1352

ABSTRACT

Purpose
Intraperitoneal (IP) cisplatin and intravenous (IV) or IP paclitaxel constitute a standard therapy for optimally debulked ovarian cancer. Bevacizumab prolongs progression-free survival (PFS) when included in first-line IV chemotherapy. In this study, the safety and feasibility of adding bevacizumab to a first-line IP regimen were assessed.

Patients and Methods
Treatment was as follows: paclitaxel 135 mg/m^2 IV over 3 hours day 1, cisplatin 75 mg/m^2 IP day 2, and paclitaxel 60 mg/m^2 IP day 8. Bevacizumab 15 mg/kg IV was given after paclitaxel on day 1 beginning in cycle 2. After six cycles of chemotherapy, bevacizumab was given every 3 weeks for 17 additional treatments. The primary end point was safety and tolerability determined by whether 60% of patients completed six cycles of IV/IP chemotherapy.

Results
Of 41 treated patients, 30 (73%) received six cycles of IV/IP chemotherapy and 35 (85%) received at least four cycles. Three (27%) of those who discontinued chemotherapy did so because of complications related to bevacizumab (hypertension, n = 2; perforation, n = 1). Grades 3 to 4 toxicities included neutropenia (34%), vasovagal syncope (10%), hypertension (7%), nausea/vomiting (7%), hypomagnesemia (7%), and abdominal pain (7%). There were three grade 3 small bowel obstructions (7%) during cycles 3, 9, and 15. One patient died following rectosigmoid anastomotic dehiscence during cycle 4. Estimated median PFS is 28.6 months (95% CI, 19.1 to 38.9 months). Three patients (7%) had IP port malfunction.

Conclusion
The addition of bevacizumab to this IP regimen is feasible; however, bevacizumab may increase the risk of bowel obstruction/perforation. The observed median PFS is similar to that seen with IP/IV chemotherapy alone.

J Clin Oncol 29:4662-4668. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Ovarian cancer is the fifth most common cause of death resulting from cancer in women.[1] Patients typically undergo primary debulking surgery. When residual disease measures ≤ 1 cm, the surgery is considered optimal. Standard adjuvant chemotherapy includes six cycles of platinum + taxane chemotherapy.[2] Regimens that include intraperitoneal (IP) chemotherapy have a survival advantage over regimens that have only intravenous (IV) chemotherapy in several randomized clinical studies.[3-5] In January 2006, on the heels of Gynecologic Oncology Group 172 (GOG-172), the National Cancer Institute (NCI) issued a bulletin promoting IP chemotherapy for patients with optimally debulked ovarian cancer.

In GOG-172, patients with optimal stage III ovarian cancer received either IV paclitaxel 135 mg/m^2 over 24 hours day 1, IP cisplatin 100 mg/m^2 day 2 and IP paclitaxel 60 mg/m^2 day 8, or IV paclitaxel 135 mg/m^2 over 24 hours day 1 and IV cisplatin 75 mg/m^2 day 2. There was a median overall survival benefit (66 *v* 49 months; $P < .001$) for IP therapy. Because of toxicity, only 42% of patients in the experimental arm were able to tolerate all six cycles delivered IV/IP; however, 80% of those in the IV arm received all six prescribed cycles.[6] The toxicity and complexity of this and other IP regimens have limited the acceptance and tolerability of IP treatment.

Vascular endothelial growth factor and other biomarkers of angiogenesis appear to correlate with prognosis in ovarian cancer.[7-9] Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor[10] and has activity against recurrent ovarian cancer.[11,12] Its role in adjuvant therapy is under investigation; the GOG-218 and ICON7 trials evaluated bevacizumab in combination with adjuvant IV carboplatin + paclitaxel.[13,14] Both studies showed a small improvement in progression-free survival (PFS) among patients assigned to bevacizumab treatment.

Safety data are needed for combining bevacizumab with IP chemotherapy before evaluating such a combination in large populations. In this study, we investigate the safety and feasibility of combining IV bevacizumab with a regimen of IV/IP cisplatin + paclitaxel.

PATIENTS AND METHODS

This single-arm phase II pilot study was performed in the outpatient setting at a single institution. It was approved by the institutional review board at Memorial Sloan-Kettering Cancer Center and reviewed annually. All patients reviewed and signed informed consent documents.

Patient Eligibility

Eligible patients were age ≥ 18 years, with stage II or III epithelial ovarian, primary peritoneal, or fallopian tube carcinoma. Patients were required to undergo primary debulking surgery, with an optimal debulking (≤ 1 cm of residual disease). Patients with borderline tumors or nonepithelial histologies were ineligible.

Other eligibility criteria included a Karnofsky performance status (KPS) ≥ 70%, adequate bone marrow (absolute neutrophil count [ANC] 1,500/μL; platelets 100,000/μL), and adequate renal (creatinine ≤ 1.5 × institutional upper limit of normal [ULN]) and hepatic (bilirubin ≤ 1.5 × ULN and AST ≤ 2.5 × ULN) function. Baseline neuropathy had to be grade ≤ 1 according to the NCI Common Toxicity Criteria (CTC).

Treatment and Dose Modifications

On day 1, patients received IV paclitaxel 135 mg/m^2 over 3 hours, followed by IV bevacizumab 15 mg/kg (beginning in cycle 2); day 2: IP cisplatin 75 mg/m^2 in 2 L normal saline; day 8: IP paclitaxel 60 mg/m^2 in 2 L normal saline (Fig 1). Standard dexamethasone and antihistamines were given before paclitaxel. Patients without disease progression or unacceptable toxicity received six cycles of therapy.

Before commencing a subsequent cycle of therapy, patients were required to have an ANC of ≥ 1,500/μL and a platelet count of ≥ 75,000/μL. If they did not meet these parameters on day 1 of a cycle, treatment was delayed and they were re-evaluated weekly until improvement. Treatment was postponed in the case of grade ≥ 2 peripheral neuropathy and was not resumed until it improved to grade ≤ 1. A creatinine level more than 1.5 mg/dL or a creatinine clearance less than 50 mL/min required dose delay. Patients in whom treatment was delayed for more than 3 weeks were removed from the study.

Dose reduction for ANC required neutropenic fever (ANC < 1.0 and T ≥ 38.5°C) or prolonged neutropenia (ANC < 1.0 for ≥ 7 days). Dose reduction for thrombocytopenia required a platelet count less than 10,000/μL or, if bleeding, 10,000 to 50,000/μL. Two dose reductions because of myelotoxicity were allowed before patients were removed from the study.

At the end of cycle 6, patients who had not exhibited progression and had not discontinued bevacizumab were eligible to continue therapy with bevacizumab (15 mg/kg) IV on day 1 every 21 days for an additional 17 cycles (maintenance therapy) or until disease progression or unacceptable toxicity.

Study End Points

The primary end point was safety and tolerability of the regimen, determined by the proportion of patients who completed all six prescribed cycles of cytotoxic chemotherapy. Patients were evaluated for safety by using NCI CTC version 3.0. Patients who had measurable disease were evaluated for response according to the GOG Response Evaluation Criteria in Solid Tumors (GOG-RECIST) guidelines. All patients were assessed with a computed tomography scan and a CA-125 measurement on completion of cycle 6. Patients with no evidence of active disease by computed tomography scan or physical examination and who had a CA-125 ≤ 35 were considered to be in complete clinical remission. CA-125 was monitored; however, it was not sufficient to determine postoperative day, which was established by radiologic or clinical progression. The secondary end point was PFS, which was defined as the time from the start of treatment to the date of disease progression or death from any cause.

Statistical Analysis

A sample size of 41 yields 90% power to accept that the proportion of patients tolerating six cycles is 60% when the true tolerability rate is 60%. The delivery of all doses of prescribed bevacizumab was not considered necessary for a patient to have achieved the primary end point.

RESULTS

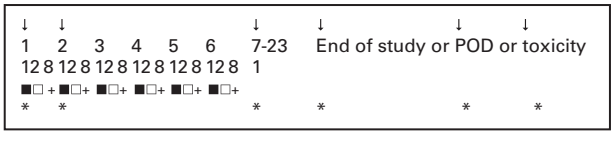
Patient Characteristics

Forty-two patients were accrued to the study over a period of 3 years, and 41 received treatment; one patient did not enter the treatment phase because her KPS fell below 70%. Demographics and baseline characteristics for the 41 treated patients are presented in Table 1. One patient was treated but subsequently was found to have been misdiagnosed (during maintenance therapy, she progressed and her true diagnosis was discovered to be pancreatic cancer); she was considered eligible for safety evaluation but not for PFS analysis. The median age of the cohort was 53 years (range, 30 to 69 years); only two patients (4.9%) were 65 years of age or older. All of the treated patients had a KPS ≥ 80%. Most patients were stage III (85.4%), and 38 (92.7%) of 41 had serous histology.

Before study enrollment, all patients underwent abdominal surgery with optimal tumor debulking. The removed tumor provided tissue for histologic evaluation and established and documented the primary site and stage.

Safety

Table 2 includes a summary of toxicities attributed specifically to bevacizumab during initial and maintenance phases. The most commonly encountered toxicities were mild (grade 1 or 2) headache or nasopharyngeal complaints, which were generally well tolerated. Hypertension was a frequent source of treatment delay; there were three episodes of grade 3 hypertension during cycles 2 to 6, but only two of



■ IV paclitaxel 135 mg/m²/3 hr on day 1
□ IP cisplatin 75 mg/m² on day 2
\+ IP paclitaxel 60 mg/m² on day 8
* IV bevacizumab 15 mg/kg on day 1, cycles 2-23
↓ Biomarker sampling
1 cycle = 21 days

Fig 1. Treatment schema. IP, intraperitoneal; IV, intravenous; POD, progression of disease.

Table 1. Patient Characteristics

Characteristic	No.	%
Population size	41	
Age, years		
Median	53	
Range	30-69	
Median KPS		90
Site (n = 40)		
Ovary	31	77
Fallopian tube	4	10
Primary peritoneal	5	12
Stage (n = 40)		
II	6	
III	34	
Grade (n = 40)		
High	37	
Intermediate	3	
Low	0	
Residual disease (n = 40)		
Visible ≤ 1 cm	28	
No gross disease	12	
Bowel resection (n = 8)*		
Small bowel	1	
Large bowel	7	

Abbreviation: KPS, Karnofsky performance status.
*All patients with bowel resections underwent primary anastomosis; no patients had stomas.

these occurred during cycles 7 to 23. Hypertension was generally more common and more severe during cycles 4 to 6.

Table 2 also summarizes grades 3 to 4 nonhematologic clinical toxicities ascribed to cytotoxic chemotherapy in cycles 1 to 6 as well as grades 3 to 4 nonhematologic laboratory abnormalities in cycles 1 to 6, which were common and included hyponatremia (15%; n = 6), hypokalemia (10%; n = 4), and hypomagnesemia (7%; n = 3). Grades 3 to 4 hematologic toxicities from cycles 1 to 6 are also listed. Myelotoxicity was generally mild, and significant events were limited to one episode of febrile neutropenia. Darbepoietin was given to 10 patients and filgrastim to five. There were 20 patients (49%) who received RBC transfusions.

Seven patients (17.5%) experienced at least one hypersensitivity reaction to paclitaxel, with three experiencing grades 3 to 4 reactions, one of whom came off study as a result. There were no hypersensitivity reactions to bevacizumab or cisplatin.

One patient died from complications of peritonitis following rectosigmoid anastomotic dehiscence during cycle 4. Intraoperatively, the site of perforation was limited to the anastomosis, and the IP port was far from the site of perforation; there was no gross tumor. This patient was counted as having experienced a bevacizumab-related grade 5 toxicity, and she is included among the 11 patients who were unable to complete the planned six cycles of IV/IP chemotherapy plus bevacizumab. In addition, three patients experienced grade 3 adhesion-related nonmalignant small bowel obstruction during cycles 3, 9, and 15. All three recovered rapidly following laparoscopic intervention, which included resection of dense adhesions. The patient who underwent repair during cycle 3 resumed IP chemotherapy on schedule, and had no additional intestinal complications. These events were considered possibly related to bevacizumab; nonetheless, only one event—the grade 5 anastomotic dehiscence—resulted in discontinuation of IP therapy and counted toward the primary end point as a failure.

One patient experienced an episode of acute vomiting and dizziness 1 month following cycle 12 (during the bevacizumab maintenance therapy). She was normotensive. A magnetic resonance imaging scan of the brain revealed evidence of intraparenchymal hemorrhage in the vermis. She was removed from study because of this grade 3 bevacizumab-related event, and her symptoms resolved with conservative management.

Tolerability

Eleven patients (27%) discontinued the study-prescribed cytotoxic regimen before cycle 7 (Fig 2). Five of these patients discontinued treatment because of cisplatin complications, two because of IP catheter dysfunction, and three because of bevacizumab toxicity. There was one grade 3/4 hypersensitivity reaction to paclitaxel, which occurred on day 1 of cycle 1.

Six patients required bevacizumab to be held during cycles 3 to 6: five times for hypertension in four patients and one time each for epistaxis and vaginal irritation. Four patients delayed initiation of bevacizumab to cycle 3 because of complications of cytotoxic chemotherapy in cycle 1.

Thirty patients (73%) received all six cycles of IV/IP chemotherapy, and 35 (85%) received at least four cycles. Crossover to a standard IV taxane + platinum combination was allowed for patients who did not tolerate the prescribed cytotoxic regimen, and 39 patients (95%) received a total of six cycles of a taxane + platinum combination, either on or off study.

No patients progressed during cycles 1 to 6. Thirty-six patients (88%) entered maintenance and received at least one dose of single-agent bevacizumab. The other five patients did not enter maintenance because of bevacizumab toxicity in cycles 1 to 6 (three), wrong diagnosis (one), or death (one). Figure 3 plots the reasons for noncompletion of maintenance. Thirteen patients (36%) received all planned doses (including two patients who skipped one cycle for vacation and elective hernia repair, respectively). Four patients (11%) had a single dose held for toxicity: mouth infection (two patients), hypertension (one), or nausea/vomiting (one). The remaining 19 patients (53%) discontinued maintenance therapy. There were 10 patients who came off study because of toxicity: arthralgias/myalgias (five patients), bowel obstruction (two), and hypertension (one), CNS hemorrhage (one), and epistaxis (one). The arthralgias were rarely more than grade 2 but interfered with quality of life to the point that patients withdrew consent. Seven patients came off study for disease progression, and one patient discontinued for elective gallbladder surgery. The mean number of doses administered in the maintenance phase was 12 (range, 1 to 17 doses).

The median time on treatment was 357 days (range, 7 to 490 days). For those who completed treatment, the median time on treatment was 469 days (range, 462 to 490 days). For those who stopped treatment because of toxicity, the median time on treatment was 232 days (range, 73 to 427 days).

Efficacy

Forty patients were assessable for the secondary end point of PFS. At the time of analysis, 23 patients (57.5%) had progressed or died and 17

Table 2. Treatment-Related Toxicities

Toxicity	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	No.	%	No.	%	No.	%	No.	%	No.	%
Bevacizumab-related toxicities										
Cycles 2-6										
Epistaxis	23	58	1	2	0		0		0	
Nasal stuffiness	26	65	0		0		0		0	
Headache	18	45	3	7.5	0		0		0	
Voice changes	7	18	0		0		0		0	
Hypertension	8	20	3	7.5	3	7.5	0		0	
Mouth pain	5	12.5	0		1	2.5	0		0	
CNS hemorrhage	0		0		0		0		0	
Bowel perforation	0		0		0		0		1	2
Bowel obstruction	0		0		1	2.5	0		0	
Cycles 7-23										
Epistaxis	13	32.5	0		0		0		0	
Nasal stuffiness	15	37.5	0		0		0		0	
Headache	14	35	0		1	2.5	0		0	
Voice changes	5	12.5	0		0		0		0	
Hypertension	2	5	0		2	5	0		0	
Mouth pain	4	10	0		1	2.5	0		0	
CNS hemorrhage	0		0		1	2	0		0	
Bowel perforation	0		0		0		0		0	
Bowel obstruction	0		0		2	5	0		0	
Arthralgias*	25	62.5	9	22.5	1	2.5	0		0	
Chemotherapy-related toxicities > grade 2, cycles 1-6										
Clinical										
Fatigue					2	5	0			
Nausea					3	7	0			
Vomiting					2	5	0			
Abdominal pain					3	7	0			
Syncope/vasovagal episode					4	10	0			
Deep venous thrombosis					0		1	2		
Laboratory										
Creatinine					0		1	2		
Hypomagnesemia					3	7	0			
Hypokalemia					4	10	0			
Hyponatremia					6	15	0			
Hematologic										
Anemia					6	15	0			
Leukopenia					7	17	1	2		
Neutropenia					9	22	5	12		
Lymphopenia					9	22	0			
Thrombocytopenia					1	2	0			
Febrile neutropenia					1	2	0			

*Arthralgias occurring during cycles 1-6 were generally attributed to cytotoxic chemotherapy, and those in later cycles were considered possibly related to bevacizumab.

(42.5%) were censored. PFS rates are presented in Figure 4. The overall median time of PFS was 28.6 months (95% CI, 19.1 to 38.9 months). The PFS rates at 12, 24, and 36 months were 90%, 55%, and 35%, respectively.

DISCUSSION

To the best of our knowledge, this is the first study to assess a regimen that included bevacizumab and IP chemotherapy, in this case IP cisplatin and IV/IP paclitaxel. It demonstrates that the addition of IV bevacizumab does not significantly impair the delivery of IP cytotoxic chemotherapy. Although the feasibility end point was met, important safety concerns were elucidated, specifically three bowel obstructions, a fatal anastomotic dehiscence, and a cerebellar bleed. PFS was a secondary end point of this study; the observed PFS of 28 months is within range of that reported in the IP/IV paclitaxel + cisplatin arm of GOG-172. The results of longitudinally collected serum biomarker studies will be reported separately.

This study was initiated after data demonstrated the efficacy of IP/IV paclitaxel + cisplatin for optimally debulked stage III ovarian cancer and of bevacizumab plus IV paclitaxel + carboplatin for stages III and IV ovarian cancer. Phase II studies revealed activity of bevacizumab in recurrent ovarian cancer—both platinum-sensitive and

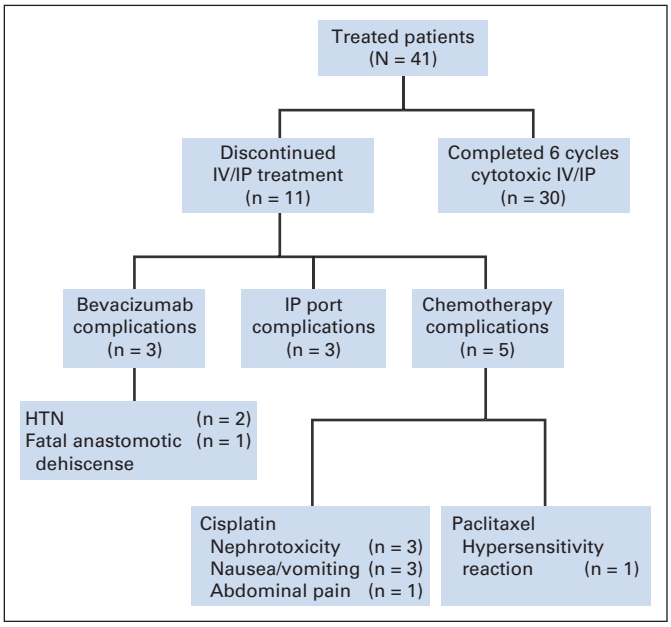


Fig 2. CONSORT diagram: Noncompletion of cytotoxic chemotherapy. Of the 39 evaluable patients, 11 (27%) did not receive the six planned cycles of IV/IP cisplatin + paclitaxel. HTN, hypertension, IP, intraperitoneal; IV, intravenous.

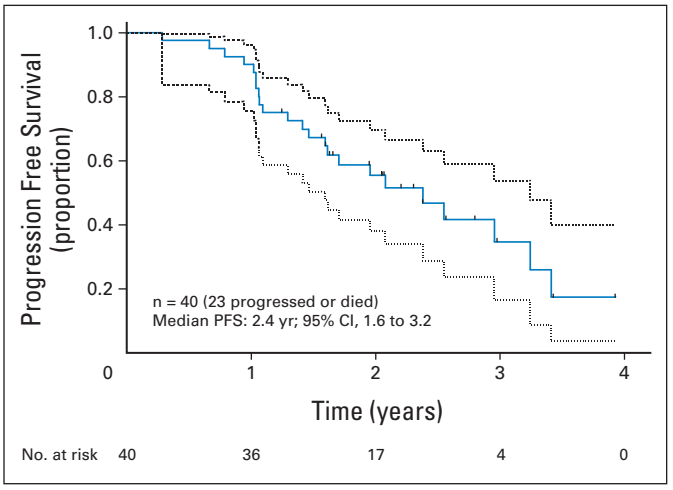


Fig 4. Estimated progression-free survival (PFS) proportion at 1, 2, and 3 years is 0.9, 0.554, and 0.3464, respectively. The estimated median PFS is 2.38 years (95% CI, 1.59 to 3.24 years). Twenty-three patients progressed or died and 17 (42.5%) were censored.

platinum-resistant cancers.[11,12] Penson et al[13] demonstrated the safety and tolerability of bevacizumab in combination with IV paclitaxel + carboplatin in first-line adjuvant therapy, followed by single-agent bevacizumab maintenance. Subsequently, two prospective randomized trials, GOG-218 and ICON7, evaluated this regimen for efficacy. Preliminary reports indicate that both trials met their statistical efficacy end points of improved PFS, although neither has yet matured to evaluate their overall survival end points.[14,15] A high likelihood of crossover therapy with bevacizumab in the patients who received placebo may ultimately confound the interpretation of the survival data.

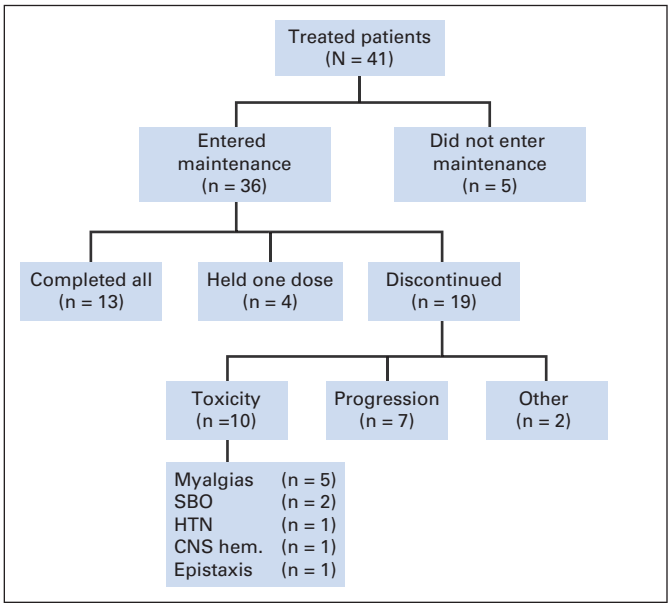


Fig 3. CONSORT diagram: Noncompletion of maintenance bevacizumab. Of the 36 evaluable patients who entered maintenance, 23 (64%) did not receive the 17 planned cycles of single-agent intravenous (IV) bevacizumab. Four of these patients missed one dose, whereas the rest discontinued treatment. CNS hem., central nervous system hemorrhage; HTN, hypertension; SBO, small bowel obstruction.

A series of pivotal trials—among them GOG-104, GOG-114/Southwest Oncology Group (SWOG) -9227 and GOG-172—demonstrated that IP cisplatin yields a survival advantage for ovarian cancer.[4,16,17] The GOG-172 showed an absolute increase in median survival of 15.9 months with the use of IP administration (65.6 months *v* 49.7 months in the IV arm; $P = .03$). This improvement came at the cost of higher toxicity. IP therapy resulted in an increase in grades 3 to 4 GI, renal, metabolic, neurologic, fatigue, and pain toxicities. Hematologic toxicities were also increased. In the IV therapy arm, 83% of patients completed six cycles of assigned therapy, and 90% completed six cycles of assigned therapy or substitution of carboplatin for cisplatin. In the IP therapy arm, however, only 42% of patients completed six cycles of assigned therapy, although 83% completed six cycles of assigned therapy or crossover to IV cisplatin or carboplatin.

The consensus is that the toxicities, inconvenience, and cost of IP therapy in general are nonetheless justified by the improved survival. More tolerable regimens are sought. For this study, the IP regimen of GOG-172 was modified in an effort to improve tolerability and enhance drug delivery. The dose of IP cisplatin was lowered from 100 mg/m^2 to 75 mg/m^2, and IV paclitaxel 135 mg/m^2 was given over 3 hours (instead of 24) and was given 1 day before cisplatin to limit neurotoxicity (as was shown in GOG-9405).[18]

This study demonstrated improved tolerability compared with GOG-172, despite the addition of bevacizumab, as evidenced by the proportion of patients completing all six cycles of prescribed cytotoxic chemotherapy (73%). This is similar to the 65% rate reported when the same regimen was given without bevacizumab.[19] Several factors may have contributed: the lower dose of cisplatin likely diminished rates of neuropathy, pain, and fatigue, and the decreased paclitaxel infusion time likely diminished the myelotoxicity. Aside from thrombocytopenia, the parameters for dose delay or reduction were at least as stringent in GOG-172 as those in this study (Appendix Table A1,

online only). The platelet cutoff did not meaningfully affect the results, since thrombocytopenia was rare in this study. Selection bias and differences in supportive care also may have played a role.

The PFS reported in GOG-172 was 23.8 months; in this study, the PFS is 28.6 months. The inclusion of stage II patients (15%; n = 6) in this study may have contributed to this disparity. Although cross-study comparisons cannot be made conclusively, the results of both studies appear to be approximately in range with each other, despite the reduced dose of cisplatin and despite the inclusion of bevacizumab.

The occurrence of a grade 5 toxicity on this study is of concern, because this regimen was adopted by the GOG and has been taken into large-scale phase III testing in GOG-252. The patient, who had undergone partial colectomy and reanastomosis as part of primary debulking, had been hospitalized during cycle 3 with severe constipation and was treated with an aggressive regimen of laxatives over several days with little effect; she developed acute peritonitis and septic shock. Intraoperatively, an anastomotic dehiscence was identified as the cause, and the event was considered possibly related to bevacizumab.

Several adhesion-related obstructions occurred in this study and are potentially attributable to this combination. Among the three patients with this complication, one had undergone large bowel resection (specifically, a modified posterior exenteration) with primary anastomosis at the time of initial debulking. It is difficult to say for certain whether primary surgery contributed to the adhesive events but the evidence suggests that it did: 20% of the patients (n = 8) on the study had initial bowel resections, and two (25%) of those patients had perforation or obstruction, although two (6%) of 32 who did not have bowel resections experienced an adhesive obstruction event. The GI perforation/obstruction rates reported in the Penson et al study,[13] GOG-218, and ICON7 were less than 3%, even given the inclusion of suboptimal patients. Furthermore, the occurrence of a high rate of adhesion-related events was not encountered, suggesting that it may be the combination of bevacizumab and IP therapy that instigated these events.[13-15]

McMeekin et al[20] reported on 22 patients treated with a regimen similar to the one in our study (excluding the day 8 IP paclitaxel), and no obstructions were reported. Although this was a smaller study with limited follow-up, the absence of IP paclitaxel may conceivably be a relevant difference. Furthermore, IP chemotherapy alone may heighten the risk: there were four major bowel complications reported among the 189 women who received IP chemotherapy in GOG-172.[6] The cerebellar bleed appears to be a direct result of bevacizumab; however, it is difficult to conceive that this was a consequence of combining bevacizumab with IP therapy.

These significant clinical safety concerns must be considered when evaluating the relative benefit of adjuvant or maintenance bevacizumab. The risks and expense of this regimen may not justify its use. Although GOG-218 and ICON7 demonstrated a PFS advantage from maintenance bevacizumab, important questions remain, including timing of initiation, duration of therapy, and whether adjuvant use endows a survival advantage. Furthermore, validated biomarkers are sorely needed to predict who is likely to incur benefit, or toxicity, from bevacizumab.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None **Research Funding:** Paul J. Sabbatini, Genentech **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Jason A. Konner, Alexia Iasonos, Sandra D. Pezzulli, David R. Spriggs, Carol A. Aghajanian
Administrative support: Diana M. Grabon, David R. Spriggs
Collection and assembly of data: Jason A. Konner, Diana M. Grabon, Scott R. Gerst, Sandra D. Pezzulli, Paul J. Sabbatini, Katherine M. Bell-McGuinn, William P. Tew, Martee L. Hensley, Carol A. Aghajanian
Data analysis and interpretation: Jason A. Konner, Diana M. Grabon, Alexia Iasonos, Howard Thaler, Sandra D. Pezzulli, Carol A. Aghajanian
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Jemal A, Siegel R, Xu J, et al: Cancer statistics, 2010. CA Cancer J Clin 60:277-300, 2010

2. Ozols RF, Bundy BN, Greer BE, et al: Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group study. J Clin Oncol 21:3194-3200, 2003

3. Alberts DS, Liu PY, Hannigan EV, et al: Phase III study of intraperitoneal cisplatin-intravenous cyclophosphamide versus intravenous cisplatin-intravenous cyclophosphamide in patients with optimal disease stage III ovarian cancer: A SWOG-GOG-ECOG Intergroup study. Int J Gynecol Cancer 6:28-29, 1996

4. Markman M, Bundy BN, Alberts DS, et al: Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: An intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 19:1001-1007, 2001

5. McGuire WP, Hoskins WJ, Brady MF, et al: Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 334: 1-6, 1996

6. Walker JL, Armstrong DK, Huang HQ, et al: Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: A Gynecologic Oncology Group Study. Gynecol Oncol 100:27-32, 2006

7. Alvarez AA, Krigman HR, Whitaker RS, et al: The prognostic significance of angiogenesis in epithelial ovarian carcinoma. Clin Cancer Res 5:587-591, 1999

8. Hollingsworth HC, Kohn EC, Steinberg SM, et al: Tumor angiogenesis in advanced stage ovarian carcinoma. Am J Pathol 147:33-41, 1995

9. Paley PJ, Staskus KA, Gebhard K, et al: Vascular endothelial growth factor expression in early stage ovarian carcinoma. Cancer 80:98-106, 1997

10. Presta LG, Chen H, O'Connor SJ, et al: Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 57:4593-4599, 1997

11. Burger RA, Sill MW, Monk BJ, et al: Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: A Gynecologic Oncology Group Study. J Clin Oncol 25:5165-5171, 2007

12. Cannistra SA, Matulonis UA, Penson RT, et al: Phase II study of bevacizumab in patients with

platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 25:5180-5186, 2007

13. Penson RT, Dizon DS, Cannistra SA, et al: Phase II study of carboplatin, paclitaxel, and bevacizumab with maintenance bevacizumab as first-line chemotherapy for advanced mullerian tumors. J Clin Oncol 28:154-159, 2009

14. Burger RA, Brady MF, Bookman MA, et al: Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study. J Clin Oncol 28:5s, 2010 (suppl; abstr LBA1)

15. Perren T, Swart AM, Pfisterer J, et al: ICON7: A phase III randomized gynaecologic cancer intergroup trial of concurrent bevacizumab and chemotherapy followed by maintenance bevacizumab versus chemotherapy alone in women with newly diagnosed epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. The 35th European Society for Medical Oncology (ESMO) Congress, Milan, Italy, October 8-12, 2010 (abstr LBA4)

16. Alberts DS, Liu PY, Hannigan EV, et al: Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 335:1950-1955, 1996

17. Armstrong DK, Bundy B, Wenzel L, et al: Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 354:34-43, 2006

18. Fleming GF, Fowler JM, Waggoner SE, et al: Phase I trial of escalating doses of paclitaxel combined with fixed doses of cisplatin and doxorubicin in advanced endometrial cancer and other gynecologic malignancies: A Gynecologic Oncology Group study. J Clin Oncol 19:1021-1029, 2001

19. Ferguson SE, Black D, Chi DS, et al: Toxicities of modified outpatient regimen of IV/IP paclitaxel and IP cisplatin in women with newly diagnosed ovarian cancer. Plenary presentation at the 38th Annual Meeting of the Society of Gynecologic Oncologists, San Diego, CA, March 3-7, 2007

20. McMeekin DD, Lanneau G, Curiel J, et al: Phase II study of intravenous (IV) bevacizumab and paclitaxel, and intraperitoneal (IP) cisplatin, followed by bevacizumab consolidation for advanced ovarian (O) or peritoneal (P) cancers. J Clin Oncol 27:287s, 2009 (suppl; abstr 5540)

